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Running title: Source-specific air pollution and systemic inflammation

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Abstract

Background: Long-term exposures to particulate matter air pollution ($PM_{2.5}$ and PM_{10}) and high traffic load have been shown to be associated with markers of systemic inflammation. Epidemiological investigations have focused primarily on total PM, which represents a mixture of pollutants originating from different sources.

Objective: We investigated associations between source-specific PM and high sensitive C-reactive protein (hs-CRP), an independent predictor of cardiovascular disease.

Methods: We used data from the first (2000-2003) and second examination (2006-2008) of the Heinz Nixdorf Recall study, a prospective population-based German cohort of initially 4,814 participants (45 to 75 years). We estimated residential long-term exposure to local traffic- and industry-specific fine PM at participants' residences with a chemistry transport model. We used a linear mixed model with a random participant intercept to estimate associations of source-specific PM and natural log-transformed hs-CRP, controlling for age, sex, education, BMI, LDL/HDL, smoking variables, physical activity, season, humidity, and city (8,204 total observations).

Results: A 1-$\mu g/m^3$ increase in total $PM_{2.5}$ was associated with a 4.53% increase in hs-CRP concentration (95% CI: 2.76, 6.33%). Hs-CRP was 17.89% (95% CI: 7.66, 29.09 6%) and 7.96% (95% CI: 3.45, 12.67%) higher in association with 1-$\mu g/m^3$ increases in traffic- and industry-specific $PM_{2.5}$, respectively. Results for PM_{10} were similar.

Conclusions: Long-term exposure to local traffic-specific PM ($PM_{2.5}$, PM_{10}) was more strongly associated with systemic inflammation than total PM. Associations of local industry-specific PM were slightly stronger, but not significantly different from, associations with total PM.

Introduction

Long-term exposure to fine particulate matter (PM) air pollution and long-term exposure to high traffic load at the residence have been associated with increased cardiovascular morbidity and mortality (Brook et al. 2010; Brunekreef et al. 2009). Furthermore, it has been hypothesized that long-term exposure to fine PM might lead to the development and progression of atherosclerosis (Bauer at al. 2010; Künzli et al. 2010; Sun et al. 2005), which has a strong inflammatory component (Libby et al. 2010). High-sensitive C-reactive protein (hs-CRP) is a widely used marker for systemic inflammation and an independent predictor of cardiovascular disease (Ridker et al. 2002). While several short-term exposure studies have reported an association between fine PM and hs-CRP (Delfino et al. 2008; Seaton et al. 1999), evidence from epidemiological studies of the long-term effects of air pollution on inflammatory markers has been inconsistent (Diez Roux et al. 2006; Forbes 2009; Hoffmann et al. 2009; Panasevich et al. 2009). One possible reason for the observed inconsistencies between studies relates to the relative toxicity of the different components or sources of the total PM mixture (Kelly and Fussell 2012), which may be greater for traffic-related emissions and metal-rich PM than other PM mixtures (Sarnat et al. 2008; Stanek et al. 2011). Several studies have reported stronger associations of cardiovascular outcomes with traffic-related fine PM than with total fine PM (Health Effect Institute (HEI) 2010). However, information regarding associations between source-specific fine PM and markers of inflammation is limited (Rückerl et al. 2011).

We aimed to estimate associations between source-specific PM and hs-CRP to gain more insight into whether the toxicity of PM air pollution varies depending on its source. To that end, we applied a chemistry transport model, using input data from detailed emission inventories, meteorology, and land use variables, to estimate the surface concentration of air pollutants. We

estimated source-specific PM concentrations by estimating total PM concentrations under alternative emissions scenarios in which contributions from individual source categories were set to zero. Since our study area is located in the Ruhr Area, an urban and industrial area in North Rhine-Westphalia, Germany, we focused on two anthropogenic sources, namely local traffic and local industry.

Methods

Study design

We used data from the baseline and first follow-up examination of the Heinz Nixdorf Recall (HNR) study, a population-based prospective cohort study. The overall study group was randomly selected from local residents' registration offices of three large adjacent cities (Mülheim, Essen and Bochum) in the Ruhr Area (also referred to as the HNR study area), aged 45 to 75 years at baseline. A total of 4,814 participants completed the baseline visit in 2000–2003, and 4,157 completed the first follow-up study visit during 2006–2008. The study design has been described in detail elsewhere (Schmermund et al. 2002). The study was approved by the institutional ethics committees and follows strict internal and external quality assurance protocols. Assessment for both, baseline and first follow-up examination included a self-administered questionnaire, face-to-face interviews for personal risk factor assessment, clinical examinations, and comprehensive laboratory tests according to standard protocols. All participants gave informed consent.

Environmental exposures

Air pollution

We used the validated time dependent three-dimensional chemistry transport model European Air Pollution Dispersion model (EURAD-CTM) (Ebel et al. 1997; Hass et al. 1993; Memmesheimer et al. 2004; Schell et al. 2001) to predict daily mass concentrations of PM with an aerodynamic diameter ≤ 10 μm (PM_{10}) and ≤ 2.5 μm ($PM_{2.5}$) on a horizontal grid resolution of 1 km. The EURAD-CTM model system is a multi-layer, multi-grid model system for the simulation of transport, chemical transformation, and deposition of tropospheric constituents (Büns et al. 2004) (for details see Supplemental Material, Air Pollution Exposure Assessment). The multi-grid system defines a sequential nesting of four horizontal grid sizes from Europe (grid size of 125 km) over central Europe (25 km), North Rhine-Westphalia in Germany (5 km) to (the south-western part of) the Ruhr Area (Duisburg-Mülheim-Essen-Bochum) (1 km) (Büns et al. 2012, Memmesheimer et al. 2004). The emission input of the model is structured with respect to different source categories according to the Selected Nomenclature for Sources of Air Pollution (SNAP-97), which, for example, includes traffic and industrial sources as different source categories. Output of the EURAD-CTM calculations includes a set of chemical compounds such as atmospheric particle mass, number density and particle size distribution and concentration of atmospheric gases, photo oxidants and a set of volatile organic compounds on a daily basis for each grid.

For sensitivity studies or emission scenarios the emission input into the EURAD-CTM can be modified or set to zero for each source category separately to study the impact of certain source categories on the concentration values (Hebbinghaus et al. 2009). We applied this method to investigate the impact of local traffic- and local industrial sources within the Ruhr Area (1 km).

To do so we first performed three different EURAD-CTM runs, which were independently of each other and differed only by emission input: 1) complete emission input, including all sources, which we will refer to as total PM (PM_{ALL}); 2) emission input, excluding emissions from local road traffic within the Ruhr Area (i.e. corresponding emission factors were set to zero) , which we will refer to as PM_{noTRA}; and 3) emission input, excluding emissions from local industry within the Ruhr Area, which we will refer to as PM_{noIND}. We then defined the concentration of local traffic-specific PM as $PM_{TRA} = PM_{ALL} - PM_{noTRA}$ and the concentration of local industry-specific PM as $PM_{IND} = PM_{ALL} - PM_{noIND}$. Since all scenarios ($PM_{ALL}$, PM_{noTRA}, PM_{noIND} were based on the same mass model equation and only differed by emission input, PM_{TRA} is an estimate of PM concentrations solely due to local traffic, and PM_{IND} is an estimate of PM concentrations solely due to local industrial sources.

The HNR study area covers a region of approximately 600 km^2 within the Ruhr Area. Hence, we were able to assign daily PM concentrations for each 1 km² grid cell to the participants' addresses (ArcView 9.2). We then calculated residential long-term exposure as a 365-day average, referring to 365 days before blood draw (for baseline and first follow-up examination). Short-and medium-term residential exposure PM refers to the average PM concentration of the last 7 and the last 28 or 91 days before blood draw, respectively.

Meteorological data

Short-term temperature, wind speed (in m/s) (north-to-south wind and east-to-west wind) and humidity refer to a moving average within 7 days before blood draw.

Noise

Long-term road noise was modelled according to the European Union directive (2002/49/EC) for the year 2005 as the weighted 24-hour mean (L_{den}) and weighted night-time (22h–6h) mean (L_{night}), using the maximum noise value in a 10m buffer around the participants' address. For 60 participants, noise values were imputed from isophone bands. Noise values were investigated as categories of 5 dB(A) with the exception of the lowest category (0–45dB(A).

Traffic

We assessed distance (meter) to highly trafficked roads, i.e. with a traffic count of > 26.000 vehicles per day (upper quintile of traffic density), using official digitized maps with a precision of at least 0.5m. The reference line was the median strip between the oncoming traffic lanes

Measurement of hs-CRP

As marker of inflammation we measured serum hs-CRP, using an automated nephelometer (BN-II, Dade-Behring Inc., Deerfield, USA). All analyses were performed in the central laboratory of the University Hospital of Essen, following a standard procedure.

Definition of covariates

Individual socioeconomic status (SES) was defined by years of education. We classified education according to the International Standard Classification of Education as total years of formal education (UNESCO 1997), using three categories (≤10, 11-13, and ≥14 (reference) years of education) for the analysis. To assess neighborhood SES the cities were divided into 106 neighborhoods according to administrative boundaries, with a median size of 11,263 inhabitants (interquartile range 7,875–16,022) Neighborhood based SES was provided by the local census authorities and included unemployment rate, welfare, mean income, retired population rate,

population density and residential stability (Dragano et al. 2009). Smoking status was defined as current, ex- and never-smoker, based on the past year. Cumulative smoking exposure was assessed for ex- and current smokers using pack years, accounting for time periods of non-smoking. Environmental tobacco smoke (ETS) was defined as any passive tobacco smoke exposure at home and/or at work (yes/no). Physical activity was assessed as times per week and categorized in three groups (<1, 1-3 and >3 times/week). Alcohol consumption was operationalized as drinks per week. Anthropometric measurements (height, weight) were conducted according to standardized protocols. Body mass index (BMI) was calculated as kg/m^2. Diabetes mellitus (DM) was defined as prior physician diagnosis of diabetes or taking an anti-diabetic drug or having a blood glucose ≥200 mg/dL or having a fasting blood glucose ≥126 mg/dL. Standard enzymatic methods were used to measure total cholesterol, high-density lipoprotein cholesterol (HDL-C). Low-density lipoprotein cholesterol (LDL-C) was measured directly (Schmermund et al., 2002). Current medications, i.e. statins, were coded according to the Anatomical Therapeutic Chemical Classification Index of the World Health Organization (Anatomical Therapeutic Chemical (ATC) Classification System 2013). All characteristics were updated at the first follow-up study visit. Coronary heart disease (CHD) at baseline was defined as a self-reported history of a myocardial infarction or coronary intervention. Incident CHD during follow-up was based on self-reported incident coronary events that met predefined study criteria (Schmermund et al. 2002), confirmed with medical records by a study end point committee (Erbel et al. 2010). We used indicator variables to model season (spring, summer, autumn, or winter according to meteorological seasons), city (Mülheim, Essen, or Bochum), and a created area variable (North, Center, or South) based on zip-codes (Hoffmann et al. 2006), which is equivalent to low, medium and high neighborhood SES.

Analytical strategy

There were 8,634 observations from 4,793 participants with complete information on exposure and hs-CRP. We excluded participants with acute infections or acute exacerbations of inflammatory disease, defined by hs-CRP >10 mg/dL, from the study population (n=5). The final data set with complete information on covariates used for analysis included 8,204 observations (in 4,665 participants, of which 3,539 supplied repeated measurements). We performed repeated measurement analysis to investigate the association between total and source-specific PM and hs-CRP using linear mixed models including a random participant intercepts to account for correlation of repeated measures. We assumed a compound symmetry covariance structure, i.e. equal variation of hs-CRP at both measurements (Box et al. 1994). Hs-CRP was log-transformed (natural logarithm) and thus results are presented as the percent-change of hs-CRP ($100 \times [\exp(\beta)-1]$).

Model 1 (M1) included a minimal adjustment of age, sex, education, BMI, and LDL-C/HDL-C. In Model 2 (M2) we additionally included lifestyle variables (smoking status, pack years, ETS, physical activity, and alcohol consumption) that predicted hs-CRP with $p < 0.10$. In Model 3 (M3) we additionally included meteorological variables (season, temperature, humidity, and wind speed) that predicted hs-CRP with $p < 0.10$. Our main analysis model (Main) therefore included age, sex, education, BMI, LDL/HDL, smoking status, pack years of smoking, ETS, physical activity, indicator variables for summer and fall (winter and spring as reference), humidity, plus city, which was included to capture spatial (unmeasured) confounding. We confirmed that covariate-outcome relationships for continuous variables (age, BMI, LDL/HDL, pack years of smoking and humidity) did not significantly depart from linearity based on likelihood ratio tests comparing models with and without squared terms ($p >0.05$).

Effect modification

We evaluated effect modification by modeling interaction terms between each exposure (modeled as a continuous variable) and age (≤65 years, >65 years), sex (men, women), ETS, CHD, intake of statins (yes, no), area (north, center, or south), city of residence (Mülheim, Essen or Bochum), and wind direction (east vs. west and north vs. south). Each potential modifier was defined according to its value at the study visit when the exposure and hs-CRP were measured. In addition, we investigated the potential modifying role of PM_{IND} (dichotomized at the 3rd quartile) on PM_{TRA} and vice versa.

Sensitivity analysis

To evaluate the robustness of our main analysis model we performed a series of models that included additional covariates. To take overall exposure levels of fine PM exposure into account when analyzing source-specific associations, we adjusted the source-specific models of PM_{TRA} and PM_{IND} for PM_{noTRA} and PM_{noIND}, i.e. PM from all other sources. We added indicators of neighborhood based SES (e.g. unemployment rate) because prior studies have observed an independent effect on various cardiovascular disease-related outcomes (Foraker et al. 2010). Furthermore we added covariates known to be associated with cardiovascular disease or with systemic inflammation, such as hypertension, diabetes, and intake of statins, to investigate robustness of our main analysis model. To account for small-scale variation in traffic-related exposures, we additionally adjusted for traffic indicator variables and road traffic noise. Furthermore, we investigated short- and medium-term (7-day and 28 or 91-day average) exposure to PM.

To evaluate the clinical relevance of exposure effects, we dichotomized hs-CRP as ≤0.3 mg/dL or >0.3 mg/dL, a cut point commonly used to denote an increased cardiovascular risk, and performed multivariable logistic regressions.

Results

Study population

The study population available for main analysis (N = 8,204 observations) (Table 1) included 4,379 participants (49.3% men) at the baseline examination with a mean age of 59.7±7.8 years and 3,825 participants (49.5% men) at the first follow-up examination. Excluded observations (N = 430) were due to missing data on the outcome, exposure or main analysis covariates and did not show systematic differences regarding exposure, outcome or covariates (data not shown). Mean values for BMI, systolic blood pressure, HDL-C did not change remarkably over time (Table 1) while LDL-C changed from borderline high values at baseline to relatively normal values at the first follow-up. Yet, we observed fewer current smokers, while the prevalence of diabetes mellitus and statin intake increased over time.

Exposure

The residential 365-day mean concentration of $PM_{2.5ALL}$ was 16.72±1.59 $\mu g/m^3$ at baseline examination (Table 2). The amount from $PM_{2.5TRA}$ was 4.8% with a mean concentration of 0.81±0.24 $\mu g/m^3$, while $PM_{2.5IND}$ contributed to 10.2% with a mean concentration of 1.70±0.94 $\mu g/m^3$. In contrast to $PM_{2.5,}$ mean concentrations for PM_{10} were noticeably higher for PM_{10ALL} (19.68±2.12 $\mu g/m^3$) and PM_{10IND} (2.47±1.46 $\mu g/m^3$), while mean concentrations of PM_{10TRA} were similar to $PM_{2.5TRA}$ (0.81±0.24 $\mu g/m^3$). At the first follow-up examination, PM concentrations were lower but showed similar patterns.

Spatial distributions of residential 365-day mean concentrations of exposure show a decreasing west-to-east-gradient in the *HNR study area* for PM_{ALL} ($PM_{2.5}$, PM_{10}) and PM_{IND} (Figure 1: A, C, D, F), while PM_{TRA} was distributed more homogeneously among cities, but clearly showing a decreasing north-to-south gradient (Figure 1: B and E). Those similarities in spatial gradients were reflected in the correlation structure: $PM_{2.5ALL}$ and $PM_{2.5IND}$ were strongly correlated, and $PM_{2.5ALL}$ and $PM_{2.5TRA}$ were only moderately correlated (Pearson correlation coefficient ρ=0.89 and ρ=0.40, respectively) (Table 3); $PM_{2.5IND}$ and $PM_{2.5noIND}$, and $PM_{2.5TRA}$ and $PM_{2.5noTRA}$ were moderately correlated (ρ=0.54 and ρ=0.27 respectively). $PM_{2.5ALL}$ and PM_{10ALL} were strongly correlated (ρ=0.99), hence correlation patterns for PM_{10} were very similar to those for $PM_{2.5}$ (data not shown).

Association of source-specific PM with hs-CRP

In our main analysis model, we estimated positive associations between hs-CRP and 1-$\mu g/m^3$ increases in $PM_{2.5ALL}$ (4.53% higher hs-CRP; 95% CI: 2.76, 6.33%) and $PM_{2.5TRA}$ (17.89% higher hs-CRP; 95% CI: 7.66, 29.09%) (Table 4). The association between hs-CRP and $PM_{2.5IND}$ (7.96% higher; 95%CI: 3.45, 12.67%) was slightly stronger than for $PM_{2.5ALL}$. In the models without adjustment for city (M1-M3), estimates for PM_{ALL} and PM_{IND} were lower. Overall, associations of hs-CRP with PM_{10} and $PM_{2.5}$ showed similar patterns.

On a population-based exposure distribution scale (using the IQR at baseline), hs-CRP was 11.06% higher (95% CI: 4.75, 17.76%) in association with an IQR increase in $PM_{2.5IND}$ (1.37$\mu g/m^3$), and 11.17% higher (95% CI: 6.73, 15.79%) per IQR increase in $PM_{2.5ALL}$ (2.39 $\mu g/m^3$). An IQR increase in $PM_{2.5TRA}$ (0.31 $\mu g/m^3$) was associated with 5.24% higher hs-CRP (95% CI: 2.32, 8.24%).

Effect modification

Generally, we observed slightly stronger associations among participants living in the north of the HNR study area compared with other areas, among participants not exposed (versus exposed) to ETS, among statin users and among those with (versus without) prevalent CHD at the corresponding examination, although confidence intervals overlapped in most analyses and interaction p-values between 0.1 and 0.5 (Figure 2). In men compared with women we observed slightly higher effect $PM_{2.5ALL}$ and $PM_{2.5TRA}$ (p-values >0.3). For $PM_{2.5TRA}$ we also observed a stronger effect in participants exposed to higher levels of $PM_{2.5IND}$ (p=0.011) and participants living in Mülheim (p=0.051) and in Essen (p=0.089). For $PM_{2.5IND}$ we additionally observed slightly stronger associations for participants living in Essen (p=0.108) and lower levels of traffic-specific PM exposure (p=0.052). We did not find indications of effect modification by age or wind direction. Patterns of effect modification for PM_{10} were similar (data not shown).

Sensitivity analysis

Adjusting for the PM concentration of all other sources ($PM_{2.5noTRA}$ or $PM_{2.5noIND}$) attenuated associations of hs-CRP with 1-$\mu g/m^3$ increases in $PM_{2.5TRA}$ (5.50% higher; 95% CI: -5.38, 17.62%) and $PM_{2.5IND}$ (3.44% higher; 95% CI: -1.45, 8.57%). In addition, the estimates became less precise. Corresponding estimates from two-pollutant models that were not adjusted for city were 12.87% (95% CI: 2.02, 24.89%) and -1.62% (95% CI: -4.67, 1.54%) for $PM_{2.5TRA}$ and $PM_{2.5IND}$, respectively. Adjusting for neighborhood indicators of socioeconomic status did not clearly change effect estimates for $PM_{2.5TRA}$, but resulted in negative associations with $PM_{2.5IND}$ (model fit did not improve) (Table 4, only adjustment for neighborhood unemployment rate is presented). Associations with PM_{10} were not affected by adjustment for neighborhood SES. Effect estimates among different sources and fractions of PM were robust towards an additional

adjustment of health indicators, such as hypertension, diabetes, or intake of statins (Table 4). Additional adjustment of the main models for proximity to traffic or road traffic noise did not influence associations (data not shown).

Associations between hs-CRP and long-term exposures (averaged over 1 year) remained robust after adjustment for short-term exposure (averaged over 7days) and increased slightly after adjustment for medium-term exposures (averaged over 91 or 28 days) (data not shown). There was also no indication of independent associations of hs-CRP with short- or medium-term exposures to PM_{ALL} or PM_{IND} (Figure 3), whereas for PM_{TRA} the positive association with hs-CRP increased with longer time windows of PM_{TRA} exposure.

In terms of clinical relevance, the odds of hs-CRP >0.3 mg/dL (the highest cardiovascular risk group) was increased in association with 1-$\mu g/m^3$ increases in $PM_{2.5ALL}$ (OR = 1.09; 95% CI: 1.02, 1.16), $PM_{2.5TRA}$ (OR = 1.43; 95% CI: 1.02, 2.00), and $PM_{2.5IND}$ (OR = 1.12; 95% CI: 0.96, 1.31).

Discussion

To our knowledge, this is the first study to analyse the association of long-term exposure to source-specific PM with a marker of subclinical systemic inflammation (hs-CRP) in the general population. Applying a novel method to estimate long-term exposure to source-specific PM ($PM_{2.5}$, PM_{10}), we observed that PM from local road traffic was more strongly associated with hs-CRP than total PM, independently of short-term exposures. The association with industry-specific PM was slightly stronger, but not significantly different from the association with total PM. We observed predominantly similar patterns in concentration and effect estimates for $PM_{2.5}$

and PM_{10}. These findings were most likely due to the almost perfect correlation of 0.99, since $PM_{2.5}$ was included in PM_{10}.

We were able to confirm previously reported long-term associations of total urban background PM with hs-CRP (Hoffmann et al. 2009) in this extended database of 8,204 observations in 4,665 participants. Our results strengthen results of prior studies reporting weak associations of medium- or long-term exposures to PM with CRP (Diez Roux et al. 2006; Zeka et al. 2006).

So far, little information, however, is available about the comparative toxicity of source-specific fractions of the PM mixture on physiological or clinical outcomes. Among others, positive associations have been reported for traffic-related PM and NO_2 with diabetes (Krämer et al. 2010), coronary heart disease hospitalization and morbidity (Gan et al. 2011), mortality (Beelen et al. 2008), and inflammatory markers (Panasevich et al. 2009). Furthermore, several studies using traffic indicators, such as traffic-density or distance to a major road, have reported associations with coronary heart disease (Hoffmann et al. 2006), atherosclerosis (Hoffmann et al. 2007; Künzli et al. 2010), diabetes (Krämer et al. 2010), and myocardial infarction (Tonne et al. 2006). One study (Bind et al. 2012), reported that short- and medium-term exposure to particle number, a measure of fresh traffic emissions, was positively associated with CRP and other markers of cardiovascular risk in a study of 704 highly selected elderly men.

These studies, however, lack the possibility to directly compare the toxicity of different sources using comparable units.

We used a novel approach to estimate source-specific PM exposures, namely exposures to local traffic- and local industry-specific PM, which enabled us to directly compare associations between hs-CRP and PM attributable to different sources. On the one hand we observed a west-

to-east-gradient for PM_{ALL} and PM_{IND}, consistent with the location of heavy industry in the west of the Ruhr Area. On the other hand, we observed a north-to-south-gradient for PM_{TRA} that was consistent with population density and the location of major arterial roads in the *HNR study area*. This finding was very interesting as it indicated the different long-term spatial patterns of these two major PM sources within our study area as well as their potential different associations with hs-CRP. The estimated effect of 1-$\mu g/m^3$ increase in local traffic-specific PM was 4-6 times stronger than the estimated effect of a comparable increase in total PM. Although effect estimates of PM_{IND} were generally slightly higher than those of PM_{ALL}, we were not able to detect a significant difference in the associations. Because of the high correlation between PM_{IND} and PM_{ALL} or PM_{noIND} and PM_{ALL}, we were not able to clearly differentiate between industry-specific and total PM.

Associations with a population-based unit of exposure, i.e. IQR, were weaker for PM_{TRA} (IQR = 0.31 $\mu g/m^3$) than for PM_{ALL} (IQR = 2.30 $\mu g/m^3$), and comparable for PM_{ALL} and PM_{IND} (IQR = 1.37 $\mu g/m^3$). Yet, PM_{TRA} estimates based on EURAD-CTM, which models mean concentrations within 1 km2, represent urban background concentrations in this area, rather than localized exposure contrasts that can be found e.g. near roads with high traffic (Zhu et al. 2002). Therefore, the IQR is an unsuitable exposure contrast for comparing estimated effects of source-specific PM in our study.

The estimated contributions of the local traffic and industry to total PM in the study area seem unexpectedly small (<5% and <11% respectively). These numbers, however, are plausible, considering that secondary or transported particles from outside the Ruhr Area are disregarded. Long range transport and formation of secondary particles in the atmosphere can contribute considerably, sometimes more than 50% depending on the meteorological situation, to the

particle mass concentration in North-Rhine-Westphalia and the Ruhr Area (Hebbinghaus et al., 2009).

We observed some heterogeneity with regard to the estimated exposure effects, when adjusting for city. While estimated effects of PM_{TRA} were robust towards the adjustment for city, estimated effects of PM_{IND} and PM_{ALL} increased considerably upon city adjustment. This finding might be a result of different spatial contrasts of specific particle concentrations within our study area, and certainly indicates the presence of residual confounding dependent on different exposure sources.

Analysis of effect modification suggested that the association between hs-CRP and PM_{TRA} was stronger in participants who were highly exposed to PM_{IND}. This is consistent with the stronger associations estimated for participants living in Mülheim, where the concentrations of PM_{IND} (because of heavy industry in neighbouring Duisburg) and PM_{ALL} were higher than in other regions of the HNR study area.

PM_{TRA} was not only more strongly associated with hs-CRP than PM_{ALL} or PM_{IND} when classified based on long-term exposure, but also when classified according to short- and medium-term time periods. We estimated stronger associations as PM_{TRA} exposure times increased. This could be due to more precise exposure estimation, or reflect a cumulative effect of PM_{TRA} on subclinical inflammation.

Limitations and strength

First, the approach of assessing source-specific air pollution is based on simulation runs and not on actual measurements. Second, we focussed on fresh local emissions in this analysis, not taking transported emissions into account, which can contribute to the local concentration by more than 50%, depending on the meteorological situation. One strength of this study is the large

and well characterized population-based, prospective cohort with repeated measures of hs-CRP and allowing comprehensive adjustment for confounding. Furthermore, we were able to take a first step into analysing source-specific emissions with a novel method that can be applied to other sources as well. We were able to model traffic-specific and industry-specific PM independently of each other and therefore could estimate associations separately for these two major anthropogenic sources of particles. In addition, source-specific exposures were modelled with a fine temporal resolution (daily concentrations) allowing the construction of different short-, medium- and long-term exposure indicators, depending on the research question.

Conclusions

In summary, we estimated source-specific PM ($PM_{2.5}$, PM_{10}) exposures in a large population-based cohort using a novel approach based on the EURAD-CTM. Our results suggest that a 1-$\mu g/m^3$ increase in long-term average exposure to fresh local traffic-specific PM was more strongly associated with hs-CRP, a marker of systemic inflammation, than a 1-$\mu g/m^3$ increase in long-term total PM, independently of short-term average exposures. Associations with local industry-specific PM were slightly stronger than associations with total PM, but we were not able to detect significant differences. Future investigations will also include the contribution of long transported source-specific emissions and different particle sizes.

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Table 1. Characteristics of the Heinz Nixdorf Recall study population at the time of the baseline (2000-2003) and first follow-up (2006-2008) study examinations.

Characteristic[a]	**Baseline (2000-2003) [N=4,379]**	**First Follow-Up (2006-2008) [N=3,825]**
Age	59.7±7.8	64.5±7.6
Male gender	2157(49.3)	1895(49.5)
hs-CRP [mg/dL][b]	0.15(0.26)	0.15(0.22)
BMI (kg/m2)	27.9±4.6	28.3±4.8
LDL-C (mg/dL)	145.7±36.3	130.9±34.7
HDL-C (mg/dL)	57.9±16.9	59.8±16.2
Systolic blood-pressure (mmHg)	132.7±20.6	134.2±19.8
CHD	300(6.9)	337(8.8)
Diabetes mellitus	611(14.0)	729(19.1)
Smoking status		
Current	1022(23.9)	678(17.7)
Ex	1515(34.6)	1533(40.1)
Never	1842(42.1)	1614(42.2)
Pack years of smoking	16.6±25.4	16±24.4
Environmental tobacco smoke	1573(35.9)	1352(35.3)
Intake of statins	468(10.7)	764(20.0)
Education		
Low	493(11.3)	386(10.1)
Medium	2438(55.7)	2145(56.1)
High	1448(33.1)	1294(33.8)
Physical activity		
Low	2261(51.6)	1859(48.6)
Medium	478(10.9)	448(11.7)
High	1640(37.5)	1518(39.7)
Unemployment rate in neighborhood	12.5±3.4	12.5±3.4
Humidity [g/kg]	6.6±2.4	6.5±2.0
Ozone	36.6±19.2	36.9±16.0
West-Wind (dominant)	1291(29.5)	956(25.0)
North-Wind (dominant)	3461 (79.0)	2956(77.3)
Season		
Spring	1189(27.7)	1054(27.6)
Summer	1240(28.3)	875(22.9)
Fall	1032(23.6)	939(24.5)
Winter	918(21.0)	957(25.0)

Characteristic[a]	**Baseline (2000-2003) [N=4,379]**	**First Follow-Up (2006-2008) [N=3,825]**
City		
Mülheim	1626(37.1)	1420(37.1)
Essen	1466(33.5)	1292(33.8)
Bochum	1287(29.4)	1113(29.1)
Proximity to traffic	1019.2±807.9	1022.8±809.8

[a]Values are mean ± SD or n (%) unless otherwise indicated. [b]Values are median (interquartile range).

Table 2. Distributions of residential concentrations of 365-day exposure to particulate matter ($PM_{2.5ALL}$, PM_{10ALL}, $PM_{2.5TRA}$, PM_{10TRA}, $PM_{2.5IND}$ and PM_{10IND}) for baseline (2000-2003) and first follow-up (2006-2008) examination.

Exposure [µg/m³] and examination	Mean	SD	Min	Max	IQR	Percentage of PM_{ALL}
$PM_{2.5ALL}$						
1	16.72	1.60	13.28	22.38	2.39	100.0%
2	15.63	1.35	12.72	21.16	2.04	100.0%
PM_{10ALL}						
1	19.68	2.12	15.60	28.15	3.12	100.0%
2	18.08	1.76	14.74	25.76	2.74	100.0%
$PM_{2.5TRA}$						
1	0.81	0.24	0.23	1.71	0.31	4.8%
2	0.57	0.16	0.17	1.26	0.22	3.7%
PM_{10TRA}						
1	0.81	0.24	0.22	1.76	0.32	4.1%
2	0.56	0.17	0.15	1.24	0.22	3.1%
$PM_{2.5IND}$						
1	1.70	0.94	0.36	5.96	1.37	10.2%
2	1.51	0.83	0.37	5.58	1.31	9.7%
PM_{10IND}						
1	2.47	1.46	0.51	9.32	2.09	12.6%
2	2.09	1.21	0.47	8.18	1.90	11.6%

Table 3. Correlation coefficient between individualized residential concentrations of 365-day exposure to particulate matter (PM_{ALL}, $PM_{TRA,}$ PM_{IND}, PM_{noTRA}, PM_{noIND}) for the baseline examination.

Exposure [µg/m³]	**$PM_{2.5TRA}$**	**$PM_{2.5IND}$**	**$PM_{2.5noTRA}$**	**$PM_{2.5noIND}$**
$PM_{2.5ALL}$	0.40	0.89	0.99	0.87
$PM_{2.5TRA}$	1.00	0.24	0.27	0.48
$PM_{2.5IND}$		1.00	0.90	0.54

Table 4. Estimated percentage difference (95% CI) in hs-CRP per 1-μg/m^3 increase in (source-specific) particulate matter (N=8,204 in 4,665 participants).

Exposure and model	ALL	TRA	IND
$PM_{2.5}$			
Model 1[a]	2.60 (1.19, 4.04)	19.46 (9.07, 30.83)	2.01 (-0.77, 4.87)
Model 2[b]	2.68 (1.26, 4.11)	17.59 (7.41, 28.73)	2.08 (-0.66, 4.90)
Model 3[c]	2.81 (1.39, 4.25)	18.70 (8.42, 29.95)	2.17 (-0.57, 5.00)
Main[d]	4.53 (2.76, 6.33)	17.89 (7.66, 29.09)	7.96 (3.45, 12.67)
Main per IQR[e]	11.17 (6.73, 15.79)	5.24 (2.32, 8.24)	11.06 (4.75, 17.76)
Main + nSES	4.47 (2.7, 6.26)	17.76 (6.92, 29.71)	-2.1 (-5.31, 1.22)
Main + DM,SysBP, Statines (N=8,197)	4.38 (2.62, 6.18)	16.85 (6.73, 27.92)	7.91 (3.39, 12.62)
PM_{10}			
Model 1[a]	1.63 (0.56, 2.71)	19.59 (9.39, 30.75)	1.1 (-0.71, 2.94)
Model 2[b]	1.73 (0.66, 2.82)	17.75 (7.75, 28.68)	1.19 (-0.60, 3.01)
Model 3[c]	1.84 (0.76, 2.92)	18.83 (8.73, 29.86)	1.25 (-0.54, 3.07)
Main[d]	3.30 (1.94, 4.69)	18.07 (8.02, 29.06)	4.60 (1.75, 7.53)
Main per IQR[f]	10.67 (6.16, 15.37)	5.46 (2.50, 8.51)	9.86 (3.70, 16.39)
Main + nSES	3.24 (1.85, 4.65)	18.01 (7.35, 29.73)	4.46 (1.59, 7.40)
Main + DM,SysBP, Statines (N=8,197)	3.19 (1.82, 4.57)	17.08 (7.13, 27.95)	4.55 (1.70, 7.48)

[a]Model 1: Age, sex, education, BMI, LDL/HDL. [b]Model 2: Model 1+smoking status, pack years of smoking, ETS, physical activity. [c]Model 3: Model 2+season, humidity. [d]Main: Model 3+city of residence. [e]$PM_{2.5ALL}$: 2.39; $PM_{2.5TRA}$: 0.31; $PM_{2.5IND}$: 1.37 [μg/m^3]. [f]PM_{10ALL}: 3.12; PM_{10TRA}: 0.32; PM_{10IND}: 2.09 [μg/m^3].

Figure legends

Figure 1. Distribution of individualized residential 365-day exposure to PM within the *HNR study area*, presented in five categories based on quintiles of distribution; A: $PM2.5_{ALL,}$ B: $PM2.5_{TRA}$, C: $PM2.5_{IND}$, D: $PM10_{ALL}$, E: $PM10_{TRA}$, and F: $PM10_{IND}$ for the study population at baseline examination time (2000-2003).

Figure 2. Effect modification for the association of $PM_{2.5ALL}$, $PM_{2.5TRA}$ and $PM_{2.5IND}$ with hs-CRP presented as percent change and 95%-CI per 1 $\mu g/m^3$. Models adjusted for age, sex, education, BMI, LDL/HDL, smoking status, pack years of smoking, ETS, physical activity, season, humidity and city.

Figure 3. Effect estimates for short-term, mid-term and long-term exposure to $PM_{2.5ALL}$, $PM_{2.5TRA}$, $PM_{2.5IND}$, PM_{10ALL}, PM_{10TRA} and PM_{10IND} on hs-CRP presented as percent change and 95%-CI per 1 $\mu g/m^3$. Models adjusted for Age, sex, education, BMI, LDL/HDL, smoking status, pack years of smoking, ETS, physical activity, season, humidity and city.

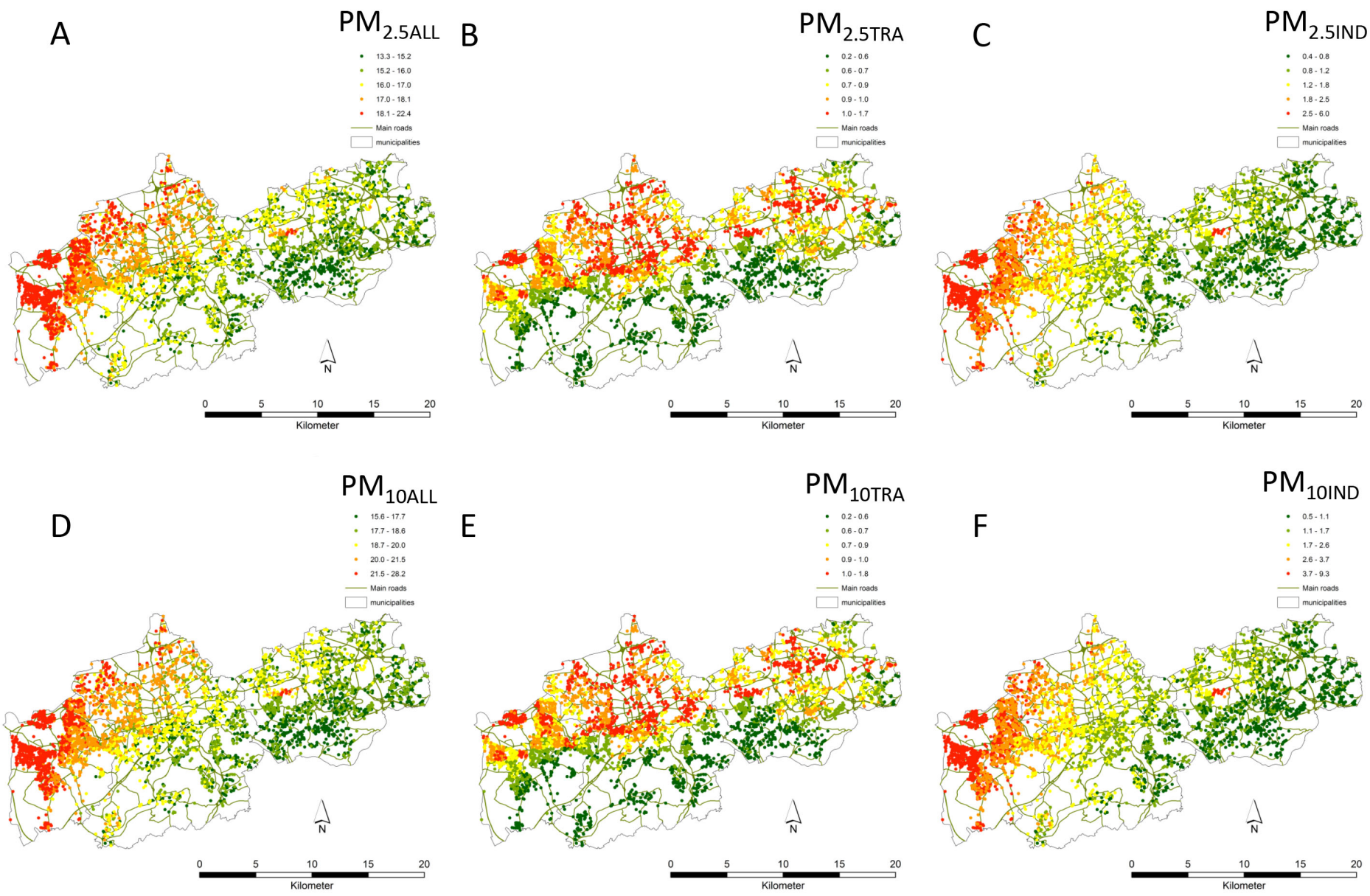
A
PM2.5ALL
13.3 - 15.2
15.2 - 16.0
16.0 - 17.0
17.0 - 18.1
18.1 - 22.4
Main roads
municipalities
N
0 5 10 15 20
Kilometer
B
PM2.5TRA
0.2 - 0.6
0.6 - 0.7
0.7 - 0.9
0.9 - 1.0
1.0 - 1.7
Main roads
municipalities
N
0 5 10 15 20
Kilometer
C
PM2.5IND
0.4 - 0.8
0.8 - 1.2
1.2 - 1.8
1.8 - 2.5
2.5 - 6.0
Main roads
municipalities
N
0 5 10 15 20
Kilometer
D
PM10ALL
15.6 - 17.7
17.7 - 18.6
18.7 - 20.0
20.0 - 21.5
21.5 - 28.2
Main roads
municipalities
N
0 5 10 15 20
Kilometer
E
PM10TRA
0.2 - 0.6
0.6 - 0.7
0.7 - 0.9
0.9 - 1.0
1.0 - 1.8
Main roads
municipalities
N
0 5 10 15 20
Kilometer
F
PM10IND
0.5 - 1.1
1.1 - 1.7
1.7 - 2.6
2.6 - 3.7
3.7 - 9.3
Main roads
municipalities
N
0 5 10 15 20
Kilometer

Figure 1

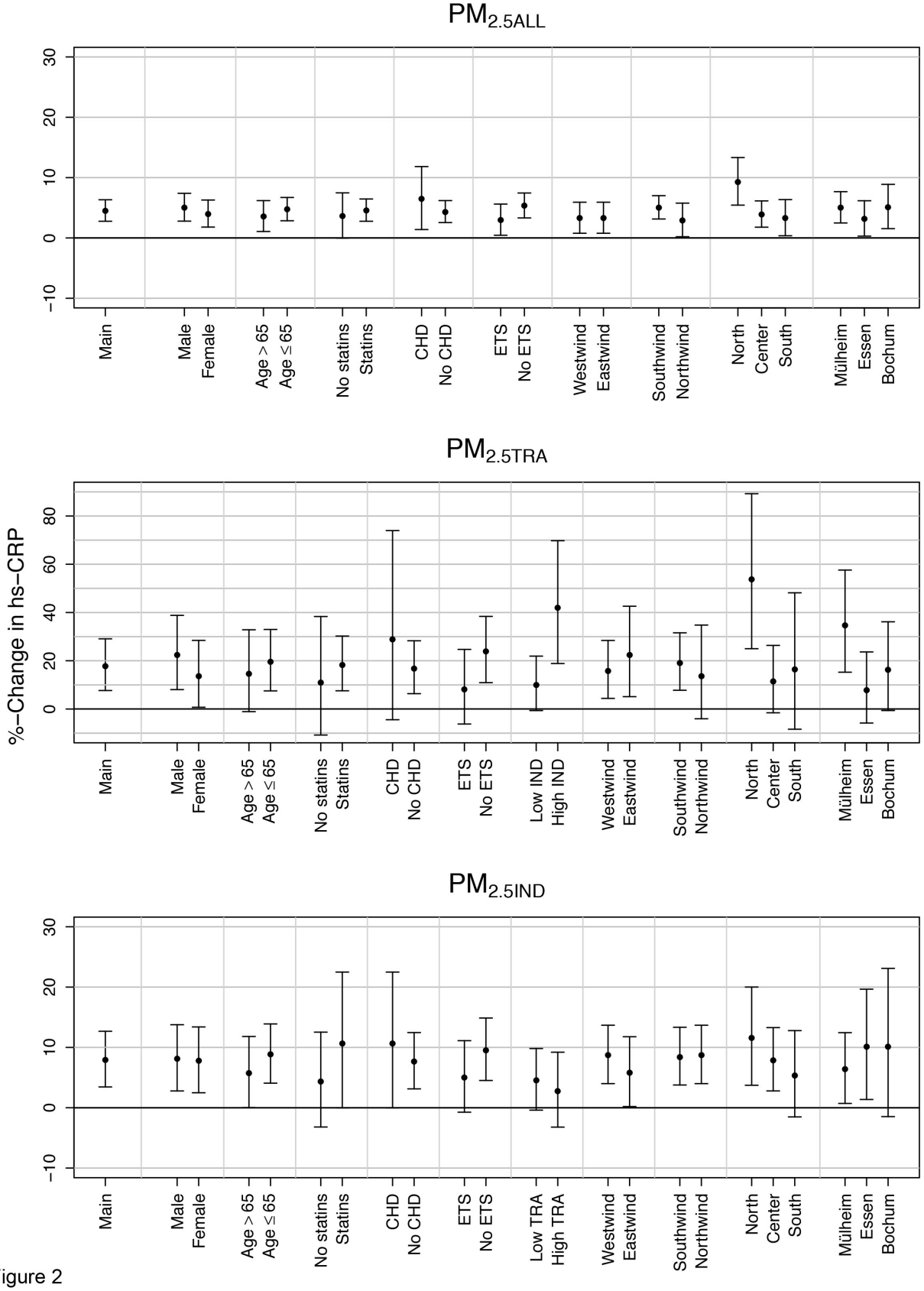
PM2.5ALL
PM2.5TRA
PM2.5IND
%–Change in hs–CRP
Main
Male
Female
Age > 65
Age ≤ 65
No statins
Statins
CHD
No CHD
ETS
No ETS
Low IND
High IND
Low TRA
High TRA
Westwind
Eastwind
Southwind
Northwind
North
Center
South
Mülheim
Essen
Bochum

Figure 2

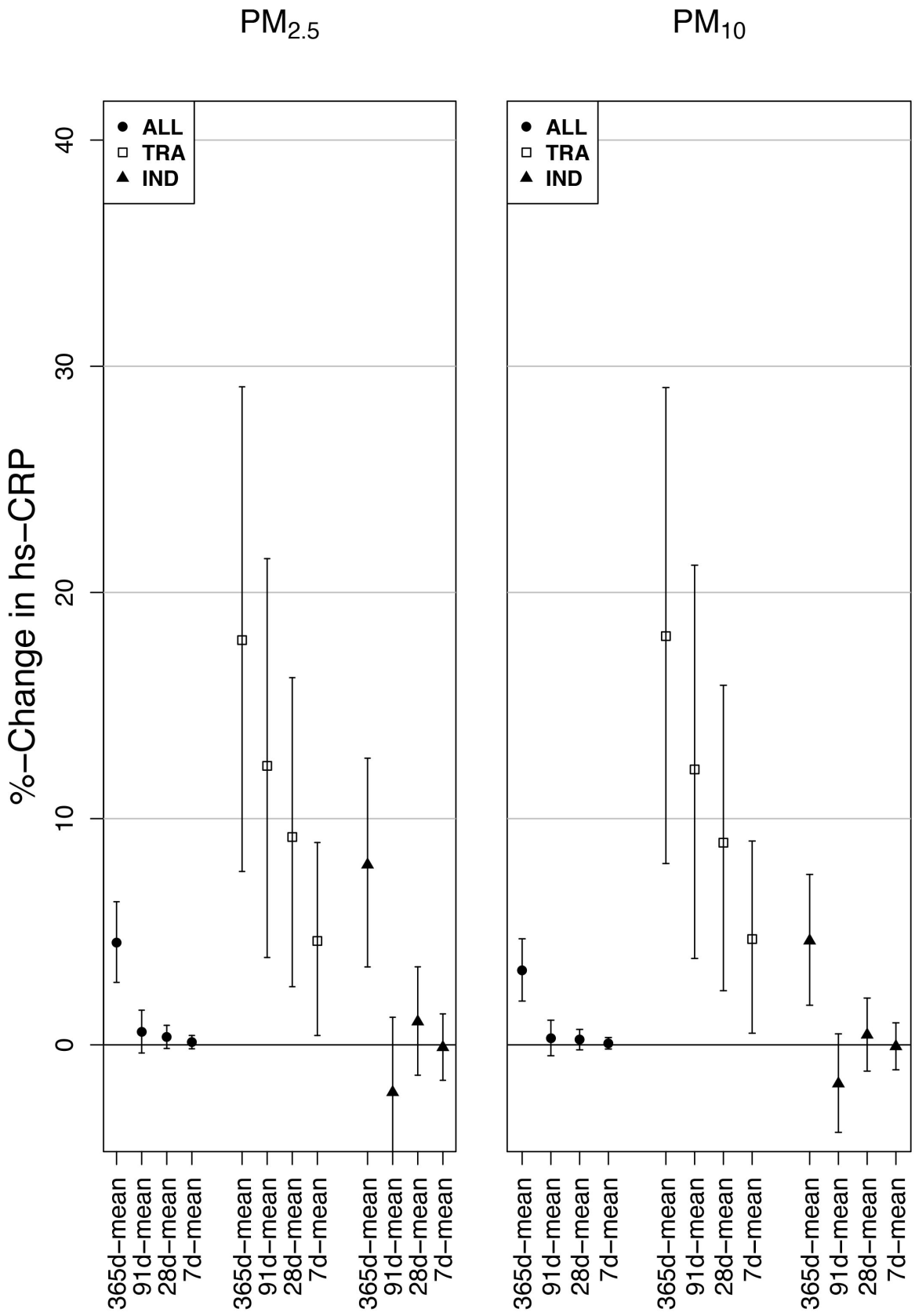
PM2.5
PM10
ALL
TRA
IND
%−Change in hs−CRP
0
10
20
30
40
365d−mean
91d−mean
28d−mean
7d−mean

Figure 3